ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

Significant progress has been made since 1981, when mysterious cases of pneumonia led researchers to identify the disease known as AIDS. Research has led to a better understanding of the structure of human immunodeficiency virus (HIV), which causes AIDS, how HIV attacks the immune system, the role of the immune system in controlling HIV infection, and how to intervene therapeutically. Potent therapeutic regimens, commonly referred to as highly active antiretroviral therapy, or HAART, have been successful in suppressing HIV to virtually undetectable levels in the blood and decreasing the incidence of opportunistic infections. HAART has greatly improved the quality of life of many HIV-infected people worldwide and has led to a dramatic decline in AIDS-related deaths.

Despite these scientific advances, the HIV/AIDS pandemic continues to rage around the world, with an estimated 39 million people living with the disease. In 2004, 3.1 million people died from AIDS, and 4.9 million people were newly infected with HIV. Of the 4.9 million new infections, 640,000 were in children. Globally, just under half of all people living with HIV are female. An estimated 40,000 people have been infected with HIV each year in the United States in the past 10 years, but the epidemic is now disproportionately lodged among African Americans and is affecting much greater numbers of women[1].

Since the beginning of the epidemic, NIAID's comprehensive research program has been at the forefront in the fight against HIV/AIDS. NIAID supports a broad array of domestic and international HIV/AIDS research programs and collaborates with more than 40 countries through investigator-initiated research grants and multicenter prevention, vaccine, and therapeutic research networks. (See Division of AIDS Overview on page 11 for a description of programs.) With a growing number of research programs and initiatives, NIAID is poised to tackle new global research challenges as well as the changing demographics of the HIV/AIDS epidemic.

Basic Research

Basic research in HIV pathogenesis, microbiology, immunology, virology, and animal model development lays the foundation for advancing research in HIV treatment and prevention. At NIAID, this research is conducted primarily through investigator-initiated research as well as a number of targeted programs and several large cohort studies.

This past year, as a result of advances in basic science, researchers have learned how virion infectivity factor (Vif) of HIV may counteract the effects of APOBEC3G, a novel antiviral protein in normal human cells that causes lethal mutations in HIV and other retroviruses. The ability of Vif to counteract the antiviral activity of APOBEC3G by targeting it for destruction helps explain Vif's importance in viral replication. Thus, interventions that either modulate levels of APOBEC3G or block its interaction with Vif are potential new targets for therapeutic interventions against HIV.

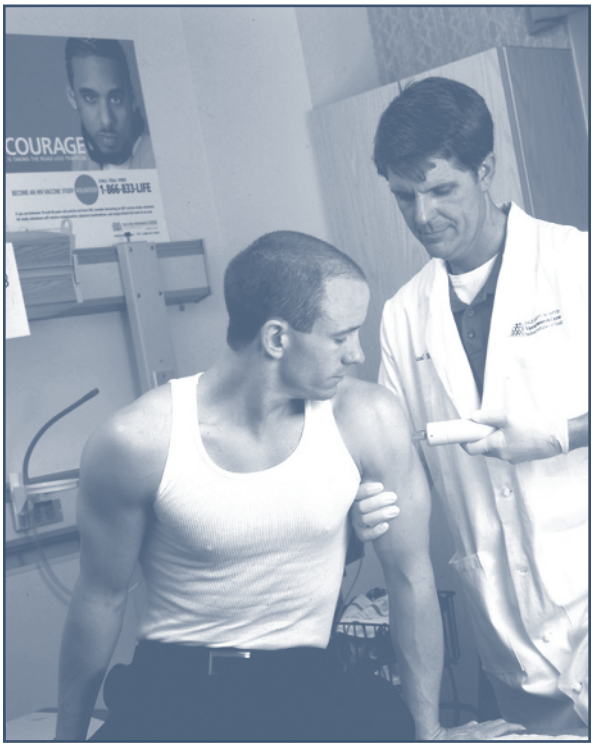
NIAID-funded investigators also found that efficient budding of HIV requires binding between a specific portion of the HIV coat and a human cellular protein called TSG101. This human protein is normally complexed with ESCRT-I and both are important components in the cell's machinery for assembling protein complexes in vesicles that transport proteins out of the cell. This discovery helps explain HIV budding and infectivity, providing new avenues for the development of drugs to inhibit HIV replication.

Several studies from the Multicenter AIDS Cohort Study (MACS) found that GB virus type C (GBV-C), a flavivirus that does not

induce disease in humans, prolongs survival of HIV-infected patients. A NIAID-supported investigator found that specific chemokine levels (RANTES, MIP-1α, MIP-1β and SDF-1) were consistently higher in GBV-C–infected peripheral blood mononuclear cells. This discovery helps explain the protective effect of GBV-C infection in HIV-positive persons.

A NIAID-funded research team identified a protein that blocks HIV replication in monkey cells. The protein, TRIM5-alpha, is the first identified to specifically target HIV's coat or capsid and inhibit viral uncoating, which is essential for the virus to reproduce. Identification of this HIV-blocking factor opens new avenues for intervening in the early stage of HIV infection, before the virus can gain a toehold, while providing insights about viral uncoating, which is a step in the viral life cycle that is not well understood and could help lead to future improvements in therapies for HIV disease.

Although much has been learned, questions still remain about (1) how HIV establishes and maintains persistent latency, (2) how HIV evades the antiviral mechanisms of the immune system, (3) the components and steps in HIV budding, (4) the protective effect of GBV-C infection in HIV infected individuals, and (5) HIV blocking factors that disrupt viral uncoating. Answering basic scientific questions about how the virus attacks the body and how the body defends itself is critical to providing additional potential targets against which therapeutic interventions and vaccines can be directed.



Demonstration of vaccination procedure on uninfected volunteer participating in a clinical trial.

Vaccine Research

An HIV vaccine that is simple to administer, inexpensive, and induces long-lasting immunity against all HIV subtypes is critical to the effective control of the global spread of HIV. It is, therefore, one of NIAID's highest priorities, albeit one of the most difficult challenges in HIV/AIDS research. NIAID supports a spectrum of HIV vaccine research and development activities, including basic research (discovery), preclinical screening and animal model development, product development and manufacturing, and clinical research. The scope and breadth of these programs and resources continue to significantly advance global HIV vaccine development efforts.

Over the years, NIAID-supported HIV vaccine research has led to the identification of new and innovative HIV vaccine designs, improvements in vaccine delivery, development of innovative laboratory techniques and animal models for evaluating vaccines, and evaluation of over 40 vaccine candidates in clinical studies. Additional studies have already been initiated or are being planned to evaluate the safety and immunogenicity of a number of new candidate vaccines, including lipopeptide vaccines alone and in combination with a canary pox vaccine, a Venezuelan equine encephalitis replicon vector vaccine, novel DNA vaccines, a recombinant nonreplicating adenovirus vaccine, modified vaccinia Ankara and other novel pox vector-based vaccines, a cytotoxic T lymphocytes multi-epitope peptide vaccine, and molecular adjuvants.

In addition, NIAID's HIV Vaccine Trials Network (HVTN), established to evaluate candidate vaccines worldwide, has been expanded to meet the demands of the growing number of candidate vaccines currently in the pipeline for which large efficacy trials may be needed. In collaboration with Merck, NIAID's HVTN is currently planning a phase IIb HIV vaccine trial to evaluate the ability of MRKAd5 HIV-1 gag/pol/nef, an adenovirus-based vaccine, to prevent infection or delay HIV disease in 1,500 high-risk volunteers. The study began enrolling volunteers at the end of calendar year 2004 in the United States, the Caribbean, South America, and Australia. Since rapidly identifying a safe and effective HIV/AIDS vaccine requires unprecedented cooperation among private sector vaccine developers, academic researchers, nonprofit organizations, and affected communities throughout the world, NIAID has established a number of collaborations and partnerships, including partnerships with other government such as the U.S. Army Medical Research and Materiel Command of the Department of Defense and non-governmental agencies. Prominently, NIAID has forged a new, innovative collaboration called the Partnership for HIV/AIDS Vaccine Evaluation (PAVE), which includes the HIV vaccine program of the Centers for Disease Control and Prevention, the U.S. Military HIV Research Program, and several nongovernmental organizations active in HIV vaccine development. PAVE will accelerate the global HIV vaccine research effort. It will also help ensure coordination and efficiency among U.S. Government agencies and their partners. These partnerships are particularly important in the conduct of research in resource-poor developing countries, which are hardest hit by the epidemic. In addition, NIAID is helping to develop Global HIV Vaccine Enterprise, an alliance of independent organizations formed to accelerate HIV vaccine development and evaluation through a shared strategic scientific plan that is implemented in a transparent, coordinated, and collaborative manner. (See the Vaccine Research and Development section on page 126 for additional vaccine information.)

Nonvaccine Prevention Research

To control the HIV/AIDS pandemic, new and more effective methods and strategies are needed to prevent HIV infection. Until a highly efficacious vaccine is developed, control of the pandemic will still require a combination of prevention approaches. NIAID's HIV Prevention Trials Network (HPTN) develops and tests promising nonvaccine strategies to prevent the spread of HIV/AIDS, including:

- Drugs or vaccines that are practical and easy to use to prevent mother-to-child transmission (MTCT) of HIV, including prevention during breastfeeding;
- Microbicides to prevent sexual transmission of HIV;
- Antiretroviral therapy (ART) that may reduce the spread of HIV from infected persons to their sexual partners;
- Measures to control other sexually transmitted diseases and thereby decrease the risk of co-infection with HIV;
- Interventions to reduce behavior that exposes people to HIV; and
- Programs to curb the spread of HIV by reducing intravenous drug use.

NIAID-funded research that makes use of the HPTN has led to important scientific advances that increase our understanding about the transmission of HIV. These findings provide a foundation for developing and testing innovative prevention strategies.

Notably, Project EXPLORE, which was an NIAID-funded, national HIV behavioral prevention trial involving nearly 4,300 men who have sex with men (MSM), reported a 20.5 percent reduction in sexual intercourse with HIV-

positive and HIV status-unknown individuals, when the experimental behavioral intervention was compared to standard individual counseling. Although the study did not find a statistical reduction in HIV infection, it underscores the need for other behavioral studies. Project EXPLORE is one of the largest behavioral studies of its kind and was designed to examine whether an intensified program of counseling on high-risk behavior helps to prevent MSM from acquiring HIV.

Prevention research involving topical microbicides is described in the Sexually Transmitted Infections section on page 114.

Therapeutics

One of the primary goals of HIV/AIDS therapeutic research is to evaluate innovative therapeutic strategies for HIV/AIDS and the complications and co-infections in all stages of HIV infection. As a result of HAART, the life expectancy of HIV-infected individuals has dramatically increased. As the number of individuals living with HIV disease increases, many develop a host of complications resulting from their therapeutic regimens, including the development of drug resistance and metabolic abnormalities and toxicities. Moreover, the immune system only partially recovers during HAART treatment. Thus, new therapies and ways to expand the clinical benefit of currently approved therapies are still urgently needed. NIAID's therapeutics research programs and networks are focusing on these issues.

In addition to a comprehensive clinical research agenda in the Unites States, NIAID fosters the study of therapy for HIV and accompanying opportunistic infections (OIs) internationally, including research in resource-poor developing countries. Key issues to be addressed in these countries include: therapeutic regimens suitable for resource-poor settings; when to start therapy; how to monitor safety and efficacy with minimal laboratory resources; interactions of endemic infections and HIV; and drug interactions, including the drugs used to treat endemic infections. Efforts are being undertaken to provide training in HIV disease and treatment for local healthcare workers in developing countries, as well as reciprocal training (or twinning) for U.S. research collaborators in the healthcare needs of developing countries. This is being accomplished through a variety of mechanisms, including the expansion of existing clinical trials groups to collaborate with investigators in developing countries, direct funding of investigator-initiated research through R01 awards, and the development of comprehensive HIV research centers through the Comprehensive International Program of Research on AIDS.

The majority of NIAID's therapeutic clinical trials are conducted through the Adult AIDS Clinical Trials Group, the Pediatric AIDS Clinical Trial Group, and the Terry Beirn Community Programs for Clinical Research on AIDS. These networks conduct, at any given time, over 100 clinical trials addressing a full range of AIDS and AIDS-related infections, complications, and co-infections. Examples of these studies include hepatitis C virus (HCV) co-infection, metabolic complications of HAART, OIs, treatment-naïve patients, salvage therapy, women-specific studies, and MTCT.

NIAID is currently implementing ACTG 5175, a large international clinical trial to evaluate the efficacy of protease inhibitors and non-nucleoside reverse transcriptase inhibitors containing therapy combinations for initial treatment of HIV-infected individuals from diverse areas of the world. In addition, NIAID continues to support two large multicenter studies, the Strategies for Management of Anti-Retroviral Therapy (SMART) study (*www.smart-trial.org*) and Evaluation of Subcutaneous Proleukin in a Randomized Interventions (ESPRIT) (*www.niaid.nih.gov/dir/labs/lir/hiv/esprit.htm*). NIAID also has several studies under way that address the timing and sequence of treatment of HIV and tuberculosis co-infection, as well as the

management and treatment of hepatitis B virus (HBV) and HCV co-infection with HIV. One such study is a phase II long-term maintenance therapy trial designed to study whether long-term maintenance with pegylated-interferon (PEG-IFN) reduces the rate of disease progression in subjects with HCV/HIV co-infection who did not respond to the standard treatment regimen of PEG-IFN plus ribavirin. Another trial is evaluating the ability of two anti-HBV drugs to control HBV infection without causing drug resistance, which is a common occurrence with chronic use of lamivudine for treating HBV infection.

NIAID continues to expand MTCT research studies internationally. Maintaining Options for Mothers Study is a prospective, randomized clinical trial evaluating the effectiveness of three different antiretroviral regimens for the prevention of nevirapine (NVP) resistance after single-dose NVP has been administered during delivery. Another important study, Optimal Combined Therapy after NVP Exposure is a phase III study that compares the response of two different classes of antiretroviral drugs in women who have received only a single dose of NVP.

NIAID also continues to evaluate new classes of antiretroviral compounds, including entry inhibitors, which show increasing promise in preclinical and clinical studies. Building on the success of the fusion inhibitor, Fuzeon, NIAID is conducting studies focused on developing an orally available drug that will fight HIV at the point of entry.

A major goal of NIAID intramural researchers and their collaborators is to discover new therapies for AIDS that are less expensive or less toxic than current therapies and can therefore be used more widely. Several such new approaches are under study in NIAID's Division of Intramural Research (DIR). For some HIV-infected patients whose plasma levels of virus have fallen to undetectable levels while on HAART, it may prove feasible to move from a continuous HAART regimen to intermittent therapy in which an individual discontinues, and then resumes, HAART in a preplanned cyclic fashion. This cyclic approach to treatment, known as structured intermittent therapy, might enable an HIV-infected person to have regular HAART-free periods while maintaining a minimal viral load and adequate levels of CD4+ T cells.

To test this concept, DIR researchers and their collaborators investigated whether short-cycle intermittent therapy consisting of cycles of a once-daily regimen of two nucleoside reverse transcriptase inhibitors—didanosine, lamivudine—and one non-nucleoside reverse transcriptase inhibitor—efavirenz—for one week, followed by a week off therapy, had a beneficial effect on patients with chronic HIV infection. Seven of 8 patients evaluated maintained suppression of plasma HIV RNA for 60–84 weeks (30–42 cycles) while preserving CD4+ T-cell counts. In addition, there was no evidence for the emergence of drug resistance to antiretroviral drugs.[2] It is important to note that the need for strict adherence to this type of regimen is necessary, and the feasibility of this approach awaits the results of randomized, controlled clinical trials underway in the United States and Africa. If safety and efficacy of short-cycle intermittent therapy is ultimately demonstrated in clinical settings, it might prove to be an important strategy to expand therapy in resource-limited settings.

Although HAART has dramatically improved the clinical outcome for many HIV-infected patients, the associated cost, toxicity, and development of drug resistance underscore the need for additional therapeutic strategies. Strategies aimed at enhancing the ability of the immune system to fight HIV infection are currently being investigated by NIAID intramural scientists as potential supplements to ART. These immune-based strategies include treatments that stimulate or suppress a particular part of the immune system, infusion of additional immune

system cells, and therapeutic immunizations. For example, NIAID's long-term basic research into the function of interleukin-2 (IL-2), a protein that stimulates CD4+ T cells to mature and multiply, and clinical studies of its safety and efficacy for HIV therapy have led to promising results. Of note, in a long-term cohort the current average IL-2 cycle frequency required to maintain their CD4+ T cell counts in the elevated range is on the order of only one cycle every 3 to 4 years. These data should lead to a much greater acceptance of intermittent IL-2 therapy as a potential adjunctive treatment in the long-term management of HIV-infected patients.[3]

Despite the development of successful therapeutic strategies, it has not been possible to eradicate HIV in infected individuals. This is due to the persistence of various viral reservoirs, including replication-competent virus, HIV-1 proviral DNA, and spliced and unspliced HIV-1 RNA in CD4+ T cells. Recent observations by NIAID scientists suggest that strategies aimed at minimizing cellular activation might further diminish residual viral replication in patients receiving HAART. In order to address this question, they have begun a pilot clinical trial to examine the safety and tolerability of a mildly immunosuppressive agent, daclizumab. The study will demonstrate whether daclizumab can normalize immunologic profiles and reduce plasma viremia in study volunteers.

The next generation of antiviral therapeutics may include compounds that prevent HIV from entering CD4+ T cells. NIAID researchers have constructed a compound that inhibits entry of HIV into CD4+ T cells and does not enhance HIV entry under any conditions. This compound is a large protein that binds specifically to the part of HIV that attaches to the CD4+ T cells. The protein exhibited extraordinarily strong binding to HIV, and relatively small amounts were able to neutralize HIV samples from a broad range of infected patients. In addition, the protein activates natural killer (NK) cells, which are an important defense against the virus. The specificity for both the HIV envelope and the NK cell receptor may promote NK cell-mediated killing of HIV-infected cells. Based on these observations, NIAID scientists are evaluating the compound for its potential as both a therapeutic agent and a vaccine adjuvant.

Current NIAID programs that support targeted drug discovery for HIV/AIDS also include: the Novel HIV Therapies: Integrated Preclinical/Clinical Program; the Innovation Grants for AIDS Research Program; the Therapeutics Research on AIDS-Associated Opportunistic Infections and Malignancies Program; the Liver and Pancreatic Disease in HIV Infection Program; the Complications of Antiretroviral Therapy Program; and the International Studies of AIDS-Associated Co-Infections Program.